PATENT
Customer No. 22,852
Attorney Docket No. 03806.0532

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	
Chin-Wen CHI *et al.*	Group Art Unit: 1614
Application No.: 10/083,565	Examiner: J. Goldberg
Filed: February 27, 2002	
For: USE OF DOCETAXEL FOR TREATING HEPATOCELLULAR CARCINOMA	

Mail Stop Appeal Brief--Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

TRANSMITTAL OF APPEAL BRIEF (37 C.F.R. 1.192)

Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on May 9, 2003.

This application is on behalf of Aventis Pharma S.A., a

☐ Small Entity ☒ Large Entity

Pursuant to 37 C.F.R. 1.17(f), the fee for filing the Appeal Brief is:

☐ $160.00 (Small Entity)

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☒ Enclosed are checks for $320.00 and $410.00 to cover the above fees.

PETITION FOR EXTENSION. If any extension of time is necessary for the filing of this Appeal Brief, and such extension has not otherwise been requested, such an extension is hereby requested, and the Commissioner is authorized to charge necessary fees for such an extension to our Deposit Account No. 06-0916. A duplicate copy of this paper is enclosed for use in charging the deposit account.

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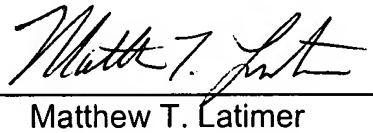
Dated: September 8, 2003

By: 

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#16
1 of 3
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9/17/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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	)	
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Application No.: 10/083,565	)	Group Art Unit: 1614
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APPEAL BRIEF

Sir:

This is an Appeal from the Final Office Action mailed January 9, 2003, in which claims 7-9, 12, and 16-22 of this patent application were rejected. No claims are allowed.

REAL PARTY IN INTEREST

The real party in interest for this Appeal and the present application is Aventis Pharma S.A.

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RELATED APPEALS AND INTERFERENCES

There are currently no appeals or interferences known to Appellant, Appellant's legal representative, or Assignee or its assigns that might directly affect, be directly affected by, or have a bearing on, the Board's decision in the present pending appeal.

STATUS OF CLAIMS

Claims 7-9 and 12-22 are pending in this application. Claims 7-9, 12, and 16-22 stand rejected, and are on appeal. Claims 13-15 stand withdrawn as directed to a non-elected invention. The claims on appeal are set forth in the attached Exhibit A. Claim 7 is the sole independent claim pending. Claims 8, 9, 12, and 16-22 depend, either directly or ultimately, from claim 7.

STATUS OF AMENDMENTS

All claim amendments have been entered.

SUMMARY OF THE INVENTION

The presently claimed invention provides a method of treating a patient suffering from hepatocellular carcinoma, a primary tumor of the liver. The method comprises intravenously administering to the patient an amount of docetaxel that is sufficient to treat hepatocellular carcinoma. (Claim 7; specification at page 2, lines 4-9 and page 3, lines 1-4.) The hepatocellular carcinoma can be, among other things, a fibrolamellar variant (claim 8; specification at page 2, lines 23-25) or a mixed hepatocellular cholangiocarcinoma (claim 9; specification at page 2, lines 23-25). Intravenous administration can be by way of intravenous infusion. (Claim 12; specification at page 3, lines 1-4.) The claimed method is based on the unexpected discovery that docetaxel is active against hepatocellular carcinomas. (Specification at page 2, lines 23-25.)

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Exemplary compositions comprising docetaxel for administration to a patient contain at least 0.01% by weight of docetaxel. Exemplary compositions for intravenous injection contain from 38 to 42 mg/ml of docetaxel. Exemplary compositions for intravenous infusion contain from 0.1 to 11 mg/ml of docetaxel. (Specification at page 4, lines 10-18.) The method of treating can comprise treating with docetaxel as the sole therapeutically active agent, or can comprise treating with docetaxel and other agents, such as other anti-neoplastic drugs. (Specification at page 4, lines 19-22.)

A typical dose of docetaxel for the treatment of humans (claim 16) is from 50 to 150 (claim 17), preferably 60 to 100 (claim 18), more preferably around 100 (claim 19) mg docetaxel/m^2 of surface area of the patient's skin. When docetaxel is administered by infusion, the rate of infusion is typically from 1 to 200, preferably around 100 mg/m^2 docetaxel per hour (claim 22). Dosing can be repeated, such as once per day, once per week (claim 20), or less often. Preferably, it is repeated every 3 weeks (claims 21, 22). (See the specification at page 5, lines 18-31.)

ISSUE

One issue is presented for review, and is on appeal. The issue is whether claims 7-9, 12, and 16-22 are patentable under 35 U.S.C. § 103(a) over Broder *et al.*

GROUPING OF CLAIMS

The claims on appeal fall into two groups. The first group consists of claims 7-9, 12, 16, 20, and 21, which recite the generic method of the invention and specific types of carcinomas, types of administration, patients, and duration of treatment. The second group consists of claims 17-19 and 22, which recite specific doses of docetaxel.

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ARGUMENTS

I. THE CLAIMED INVENTION IS PATENTABLE OVER *BRODER* BECAUSE *BRODER* DOES NOT PROVIDE A MOTIVATION TO TREAT HEPATOCELLULAR CARCINOMAS INTRAVENOUSLY WITH DOCETAXEL

The Examiner has rejected claims 7-9, 12, and 16-22 as unpatentable under 35 U.S.C. § 103(a) over Broder *et al.* (U.S. Patent No. 6,245,805 B1; "*Broder*"). The Examiner admits that *Broder* "only shows treatments with oral administration while the claims are directed to intravenous administration." (Office Action of July 30, 2002, at page 3.) However, the Examiner concludes that *Broder* provides sufficient motivation to achieve the presently claimed method of treating hepatocellular carcinoma, which requires intravenously administering docetaxel to a patient in an amount sufficient to treat hepatocellular carcinoma.

It is well established that, in order for the Examiner to set forth a *prima facie* case of obviousness, there must be some teaching, motivation, or suggestion, either in the reference relied upon by the Examiner or in the knowledge generally available to one of ordinary skill in the art, to modify the cited art to achieve the presently claimed invention. See, for example, MPEP §§ 2143 and 2143.01. Furthermore, it is well established that the art relied upon to reject the claims must be considered as a whole, and that disclosures that teach away from the claimed invention must be considered when determining obviousness. MPEP § 2145.

In supporting the rejection of the pending claims, the Examiner relies on *Broder's* statements that "among the types of carcinoma which may be treated effectively with oral paclitaxel, docetaxel, other taxanes and their prodrugs and derivatives are hepatocellular carcinoma" (Col. 15, lines 40-45). See the Final Office Action at page 3.

The Examiner relies on these statements to infer that success in orally treating hepatocellular carcinoma would motivate one of ordinary skill in the art to treat the same cancer by intravenous administration of the same compounds, including docetaxel. However, the statements relied upon by the Examiner must be put in context.

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First, the references to oral paclitaxel and other taxanes refer not only to the active compounds alone but to the necessary presence of an oral bioavailability enhancing agent, notably cyclosporin. Paclitaxel is very poorly absorbed when administered orally (less than 1%). Other sources indicate 0%. See *Broder*, Col. 10, lines 1-9. *Broder* then states:

> Moreover, no effective method has been developed to enable the effective administration of oral paclitaxel . . . or of other oral taxanes or paclitaxel analogs such as docetaxel which exhibit antitumor activity. For this reason, paclitaxel has not until now been administered orally to human patients, and certainly not in the course of treating paclitaxel-responsive diseases. *Id.* at lines 9-16.

What this paragraph says is that, at the time of *Broder's* invention, paclitaxel or docetaxel could not be administered orally by itself. It also says that oral paclitaxel had not been used to treat any paclitaxel-responsive diseases. Therefore, when *Broder* says that "among the types of carcinoma which may be treated effectively with oral paclitaxel, docetaxel, other taxanes and their prodrugs and derivatives are hepatocellular carcinoma" (Col. 125, lines 40-44), the emphasis has to be on the "may" of "may be treated", because, in fact, hepatocellular carcinoma had not been treated using oral paclitaxel, or docetaxel. Moreover, hepatocellular carcinoma is not identified by *Broder* as one of the cancers for which paclitaxel, parenterally administered, has been effective or potentially could be effective. See *Broder*, Col. 9, lines 29-40. Therefore, there is no teaching in *Broder* or oral or parenteral use of paclitaxel for hepatocellular carcinoma, nevermind docetaxel. In fact, the suggestion that oral paclitaxel "may" be used to treat hepatocellular carcinoma would not motivate one of ordinary skill in the art because the facts, even as expressed in *Broder*, teach otherwise.

In the second statement relied on by the Examiner (the "method of the invention, in selectively producing high blood concentrations of antitumor agents is particularly valuable in the treatment of liver cancer including, e.g., hepatocellular carcinoma and live metastases"), the

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method cannot refer to the oral administration of paclitaxel or taxanes alone. That method produces 0-1% absorption in the blood. Indeed, *Broder* is directed to improving the oral bioavailability of pharmaceutical agents that are poorly absorbed in the gastrointestinal tract by combining them with cyclosporins. See *Broder* at Col. 4, lines 20-36. Therefore, the "method" must refer to the co-administration of taxane and an oral bioavailability-enhancing agent, such as cyclosporin.

Present independent claim 7 recites:

> 7. A method of treating hepatocellular carcinoma, said method comprising administering to a patient docetaxel in an amount sufficient to treat said hepatocellular carcinoma, wherein said administering is intravenous.

The claimed method requires intravenous administration of docetaxel in an amount sufficient to treat hepatocellular carcinoma. It does not recite the oral co-administration of docetaxel and cyclosporin, as required by *Broder*. It recites intravenous administration of docetaxel alone. Although claim 7 is "open" to other compounds, it is not open to compounds that are incompatible with intravenous administration. Because intravenous administration is claimed, one of ordinary skill in the art would not be motivated to add an oral bioavailability enhancing agent as taught by *Broder*. Nor would one of ordinary skill in the art be motivated to use docetaxel by itself because *Broder* teaches that is ineffective.

Appellants submit that, at the time of the present invention, *Broder* would not have motivated one of ordinary skill in the art to treat hepatocellular carcinoma by intravenous administration of docetaxel. Here the portions of *Broder* relied upon by the Examiner would not teach or suggest to one of ordinary skill in the art that docetaxel by itself could be used to orally treat any cancer, let alone hepatocellular carcinoma. There would be no reasonable expectation of success and therefore, there would be no motivation in *Broder* to use docetaxel alone intravenously for treatment of that particular cancer.

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Indeed, the disclosure of *Broder*, taken as a whole, teaches away from treating hepatocellular carcinoma by intravenously administering docetaxel. For example, *Broder* states at column 16, lines 28-46:

> Apart from the higher than previously achieved local concentration of the active ingredients in the liver, the plasma and tissue distribution of the active target agents administered orally with the appropriate enhancing agents as provided in the present invention is remarkably and surprising similar to that observed upon IV administration. A series of studies with experimental animals showed that steady state plasma levels of paclitaxel were achieved upon oral co-administration with CsA by the third day of the regimen. The levels of the target agent achieved at steady state were comparable to those achieved in patients by a 96-hour IV infusion of paclitaxel. A 27% response rate was found in taxane-failure patients with metastatic breast cancer treated with a continuous 96-hour infusion every three weeks (Seidman et al., *J. Clin. Oncol.*, 14:1877, 1996). It is believed that similar results can be achieved with the treatment methods of the present invention, without the discomfort, inconvenience and risks of prolonged IV infusions.

This passage from *Broder* indicates that, to achieve a higher level of paclitaxel in the liver, one must deliver it according to *Broder's* invention. In other words, *Broder* teaches that, to achieve a higher level of paclitaxel in the liver, oral co-administration of the paclitaxel in a formulation according to the invention is necessary. This disclosure would discourage one of ordinary skill in the art from attempting to treat a hepatocellular carcinoma by intravenous administration of docetaxel. Indeed, it teaches away from treating hepatocellular carcinoma by intravenous administration of docetaxel. A disclosure that teaches away from the claimed invention is a significant factor to be considered in determining patentability. MPEP § 2145.

For at least the reasons set forth above, Appellants submit that *Broder* does not provide the requisite motivation to treat hepatocellular carcinoma intravenously with docetaxel in an amount sufficient to treat the carcinoma. Accordingly, Appellants submit that the Examiner has failed to satisfy the requirements for a *prima facie* case of obviousness of claims 7-9, 12, and 16-

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22 under 35 U.S.C. § 103(a) over *Broder*. Therefore, Appellants submit that claims 7-9, 12, and 16-22 are patentable under 35 U.S.C. § 103(a) over *Broder*.

II. THE CLAIMED INVENTION IS PATENTABLE OVER *BRODER* BECAUSE *BRODER* DOES NOT PROVIDE A REASONABLE EXPECTATION OF SUCCESSFULLY INTRAVENOUSLY TREATING HEPATOCELLULAR CARCINOMA WITH DOCETAXEL

In rejecting claims 7-9, 12, and 16-22 as unpatentable under 35 U.S.C. § 103(a) over *Broder*, the Examiner asserted that there would be "a reasonable expectation that said docetaxel would be effective." (Office Action of July 30, 2002, at page 3.) However, the Examiner has not explained, in any Office Action, why or how one of ordinary skill in the art at the time of the present invention would have had this asserted reasonable expectation. Appellants submit that the Examiner's assertion is not only unsupported, and thus improper, but is not, in fact, supported by the state of the art at the time of the present invention. For at least these reasons, the Examiner has failed to set forth a *prima facie* case of obviousness based on *Broder*.

The only data presented by *Broder* that could possibly be considered relevant to treatment of hepatocellular carcinoma are data showing that paclitaxel can be found in the liver after it is co-administered with cyclosporin to a subject. However, these data do not show that the paclitaxel is present in an amount sufficient to treat hepatocellular carcinoma (*i.e.*, in an effective amount). Furthermore, they do not show that an effective amount of paclitaxel can be localized to the liver. Indeed, it would have been surprising if *Broder* had shown that an effective amount of paclitaxel was localized in the liver and effectively treated hepatocellular carcinoma in view of the widely-held belief at the time of the present invention and now that paclitaxel is not effective against hepatocellular carcinoma. (See the present specification at page 1, lines 18-21; and Exhibits B, C, and D.)

More specifically, Exhibit B is a 1998 Phase II study of paclitaxel therapy for hepatocellular carcinoma patients. The conclusion of the study was that paclitaxel given

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intravenously in a dose of 175 mg/m^2 over three hours "has no significant anti-cancer effect in HCC patients" and that it should be used with caution in cancer patients with liver impairment. Chao *et al.*, *British Journal of Cancer* **78**(1):34-39 (1998), Abstract.

Exhibit C (Fong, Y. *et al.*, *"Cancer of the Liver and Biliary Tree"*, in Cancer Principles & Practice of Oncology, 6th Ed., Lippincott Williams & Wilkins, Chapter 33.5 (2001)) discusses the state of the art at about the time of the present invention. In particular, it shows that attempts to treat hepatocellular carcinoma with paclitaxel had been generally unsuccessful (see Table 33.5-8, page 1171), and concludes that "of the published randomized studies on HCC, neither doxorubicin nor any chemotherapeutic agent used singly or in combination has been shown to have any survival benefit for HCC patients." *Id.* at page 1171. (Appellants note that, at the time of publication of this reference, no studies had been published showing that docetaxel could be effectively administered to treat HCC. Thus, the conclusion, while applicable to the teachings of *Broder*, is not directly applicable to the presently claimed invention.)

Exhibit D (Lin, H-L *et al.*, *British Journal of Cancer* 88(6):973-980 (2003)) shows that even as of 2003, taxol (paclitaxel) alone had not been shown to be effective in treating hepatocellular carcinoma. More specifically, Lin *et al.* shows in Figures 6A and 6B, and the accompanying text on page 978, left column, that treatment of hepatocellular carcinoma cells in a mouse model was not possible using taxol alone. Like *Broder's* data relating to oral delivery of active agents for treatment of hepatocellular carcinoma, Lin *et al.* shows that effective treatment is only possible when taxol is co-administered with cyclosporin A.

The fact that paclitaxel was (and still is) believed to be ineffective against hepatocellular carcinoma, coupled with the deficiencies in the data of *Broder* to refute this belief, would have precluded one of ordinary skill in the art from reasonably concluding that paclitaxel can be administered, orally or intravenously, in an amount sufficient to treat hepatocellular carcinoma.

Furthermore, and most importantly, the data of *Broder* do not show, or even suggest, that docetaxel can be administered to a patient in an amount sufficient to treat hepatocellular carcinoma. In order for such a conclusion to have been reasonably drawn, one of ordinary skill

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in the art must have been able to conclude from *Broder* that the mere presence of paclitaxel in the liver indicates not only that docetaxel could also be localized to the liver, but that docetaxel would be active against hepatocellular carcinoma (whereas paclitaxel is not), and that a sufficient amount of docetaxel could be delivered to the liver to achieve treatment of the carcinoma. Appellants submit that such a conclusion is not reasonably supported by the data and general disclosure of *Broder*.

It was well known in the art at the time of the present invention that docetaxel and paclitaxel had different pharmacological properties, and that one could not assume that either would have a particular pharmacological property in common with the other. (See, for example, Exhibit E, which states that plasma clearance of paclitaxel exhibits nonlinear kinetics, whereas plasma clearance of docetaxel shows linear kinetics, and that the toxic effects of the two differ (Abstract, page 22; pp. 24-27), and combination therapies that include docetaxel or paclitaxel have different efficacies (p. 27).) Thus, because of the different pharmacological properties of paclitaxel and docetaxel, one of ordinary skill in the art would not have been able to draw any reasonable conclusion regarding docetaxel based on the paclitaxel data presented by *Broder*.

In addition, it was widely believed at the time of the present invention that paclitaxel and docetaxel had similar tissue specificities. See, for example, Exhibit F, page 70, first full paragraph of right column; and Exhibit G, page 394, "Antitumor Activity" section. Thus, if one were, for some reason, to disregard the differences in pharmacological properties between paclitaxel and docetaxel, one might conclude that docetaxel, like paclitaxel, could be found in the liver after administration.

However, as discussed above, it was widely believed in the art at the time of the present invention that paclitaxel was not active against hepatocellular carcinomas (see Exhibits B and C, discussed above.) This belief is consistent with the disclosure of the present specification, which states that the present invention is directed to the unexpected discovery that docetaxel can be used to treat hepatocellular carcinoma. (Specification at page 2, lines 23-25.) Thus, even if one of ordinary skill in the art were to somehow have expected docetaxel could be localized to the

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liver, that person would have likely expected it to have the same or a similar effect on hepatocellular carcinoma as paclitaxel - no effect.

Thus, the disclosure of *Broder* of the mere presence of detectable quantities of paclitaxel in the liver obtained by oral co-administration of paclitaxel and a cyclosporin would not have provided one of ordinary skill in the art with a reasonable expectation of successfully treating hepatocellular carcinoma by administering docetaxel intravenously. Appellants submit that the failure of *Broder* to provide such a reasonable expectation of success precludes the Examiner from setting forth a *prima facie* case of obviousness against claims 7-9, 12, and 16-22 under 35 U.S.C. § 103(a) over *Broder*. Accordingly, Appellants submit that claims 7-9, 12, and 16-22 are patentable under 35 U.S.C. § 103(a) over *Broder*.

III. THE CLAIMED INVENTION IS PATENTABLE OVER *BRODER* BECAUSE *BRODER* PROVIDES NO MOTIVATION OR EXPECTATION OF SUCCESS TO SELECT THE DOSES RECITED IN DEPENDENT CLAIMS 17-19 AND 22

Claims 17-19 and 22 are separately patentable over *Broder*. Appellants submit that *Broder* fails to motivate one of ordinary skill in the art to achieve the doses specifically recited in present claims 17-19 and 22, and fails to provide a reasonable expectation that such doses would be suitable for intravenous administration of docetaxel. More specifically, claims 17-19 and 22 recite defined doses. In rejecting these claims, the Examiner has not addressed these specific doses. During prosecution, Appellants timely traversed this aspect of the rejection, and provided scientific reasoning supporting their position that the oral doses disclosed by *Broder* would not suggest the appropriate doses for intravenous administration or provide a reasonable expectation that the doses disclosed by *Broder* would be appropriate for intravenous administration of docetaxel to treat hepatocellular carcinoma. Appellants submit that the Examiner has not refuted Appellants' position on this issue. Indeed, the Examiner has not addressed this issue since first raising it in the Office Action dated July 30, 2002. In the absence of a motivation and reasonable expectation provided by *Broder*, Appellants submit that the invention presently claimed in

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claims 17-19 and 22 is not rendered obvious by *Broder*. Accordingly, Appellants submit that claims 17-19 and 22 are patentable under 35 U.S.C. § 103(a) over *Broder*.

IV. THERE SHOULD BE NO REQUIREMENT FOR A SIDE-BY-SIDE COMPARISON

The Examiner has stated that "[c]learly, a side-by-side comparison of the oral administration vs. the intravenous administration [of docetaxel] is needed." Final Office Action at page 3. Appellants submit that such a showing is not necessary because 1) the Examiner has failed to set forth a *prima facie* case of obviousness, and 2) the state of the art does not support the conclusions drawn by the Examiner regarding the teachings of *Broder*.

It is well established that the Examiner carries the initial burden to set forth a *prima facie* case of obviousness against a rejected claim. It is only after the Examiner has satisfied his burden does the burden shift to the applicant to show that the rejected claim is not obvious. MPEP § 2142. In the present case, as discussed above, the Examiner has failed to show that *Broder* provides a motivation for, or reasonable expectation of success in, treating hepatocellular carcinoma by intravenous administration of docetaxel. For at least this reason, no "side-by-side" comparison (*e.g.*, submission of data by Appellants) is necessary. Therefore, Appellants submit that the Examiner's requirement for a "side-by-side" comparison is improper.

V. CONCLUSION

For all of the reasons discussed above, Appellants respectfully submit that claims 7-9, 12, and 16-22 define patentable subject matter over *Broder*. Therefore, Appellants respectfully request that this Honorable Board reverse the rejection of claims 7-9, 12, and 16-22, and permit this application to issue as a U.S. patent.

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To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is respectfully requested. If there is any fee due under 37 C.F.R. § 1.16 or §1.17 that is not submitted with this Appeal Brief, please charge the fee to our Deposit Account No. 06-0916. This Appeal Brief is being submitted in triplicate.

Respectfully submitted,

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Attachments:
Exhibits A-G

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